REMARKS

Claims 114 to 132 were pending in the present application.

Claims 114-119 and 122-131 have been amended to clarify the claimed invention. Claim 121 has been cancelled without prejudice. Applicants reserve the right to prosecute the subject matter of claim 121 in one or more related continuation, divisional, and/or continuation-in-part applications. Claims 114-119 have been amended to remove redundant and other recitations of amino acid sequences from the claim.

Claims 115, 116, 118, 119, and 122 have been amended to clarify that the percentage of identity is the percentage of amino acid residues that are identical between the two sequences in an alignment. Support for this amendment can be found at page 15, line 36 to page 16, line 2. Claim 115 has been further amended to correct a clerical error: "amino sequence" has been amended to read "amino acid sequence."

Claim 117 has been amended to recite "the carboxy-terminal 188 amino acids of SEQ ID NO:29." Support for this amendment can be found in the specification as filed at page 12, line 21 and line 26.

Claim 122 has been amended to recite a sequence identity of 97% and that the claimed protein can be bound by an antibody that binds to a protein of claims 114, 115, or 116. Support for this amendment can be found in the specification as originally filed at page 15, line 35 to page 16, line 1; page 8, lines 8-9; and page 11, lines 3-7 and lines 20-30.[1]

Claims 123, 124, 125, 126, and 128 have been amended to delete several dependencies, due to claim cancellations or failure to further limit the claim depended upon.

Claim 127 has been amended to recite that the polynucleotide encodes a protein that displays inhibitory activity in an NIH 3T3 fibroblast spreading assay. Support for this amendment can be found at page 11, lines 20 to 30; page 17, lines 6-7; in Example 6.1.10, beginning at page 59; and in Example 6.2.7, beginning at page 67. Claim 127 has also been amended to recite a washing step that can be used to test whether a particular nucleic acid sequence falls within the scope of the claim. Support for the amendment can be found in the

[1] It is noted that SEQ ID NO:32 has been corrected in the replacement Sequence Listing submitted concurrently herewith.

specification as originally filed, *e.g.*, at page 14, lines 2-4. Claim 127 has further been amended to capitalize the trademark Ficoll® in accordance with M.P.E.P. § 608.01(v).

Claim 129 has been amended to recite that the recombinant host cell resides *ex vivo*. Support for the amendment can be found in the specification as filed at page 39, lines 2-29, particularly, at line 28. Claims 130 and 131 have been amended to clarify that "it" refers to the recombinant host cell.

New claims 133-137 have been added. Support for new claim 133 can be found in the specification as originally filed, *e.g.*, at page 25, lines 8-17. Support for new claims 134 and 135 can be found in the specification as originally filed, *e.g.*, at Figure 13; page 10, lines 1-21; page 15, line 28 to page 16, line 4;[2] page 68, Table 2; original claim 16;[3] and page 17, lines 26-32.[4] Support for new claims 136 and 137 can be found in the specification as originally filed at page 17, lines 26-27[5] and at page 16, line 1. Support for claims 134-137 can further be found at page 11, lines 11-16 and at page 25, lines 30-33.

Thus, the claim amendments do not introduce new matter. Claims 114-120 and 122-137 will be pending upon entry of the present amendments.

A replacement Sequence Listing is provided herewith. In the description of Figure 14 at page 8 of the specification, it is indicated that the amino acid sequence of rat Nogo C corresponds to SEQ ID NO:32. The description of Figure 14 further indicates that rat Nogo C is depicted in Figure 14. The START and STOP of the open reading frame are clearly marked in Figure 14. The length of the open reading frame is 199 amino acids, as is disclosed in the specification at page 12, line 27 for Nogo C. SEQ ID NO:32 in the previously submitted Sequence Listing, however, does not correspond to the amino acid sequence of rat Nogo C as set forth in Figure 14. Accordingly, the presently submitted replacement Sequence Listing sets forth the correct amino acid sequence for rat Nogo C as SEQ ID NO:32. Thus, the replacement Sequence Listing includes no new matter.

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[2] It is noted that the recitation of SEQ ID NO:30 in the specification as filed was amended to recite SEQ ID NO:29 in the Preliminary Amendment under 37 C.F.R. § 1.115 filed October 21, 2002.

[3] See footnote 2 supra.

[4] See footnote 2 supra.

[5] See footnote 2 supra.

1. THE OBJECTION TO THE CLAIMS SHOULD BE WITHDRAWN

Claims 114-119 and 123-125 have been objected to because certain sequences are listed twice in each of these claims. Claims 114-116 recite SEQ ID NO:2 and residues 1-1163 of SEQ ID NO:2, which are identical sequences; claims 117-119 recite SEQ ID NO:29 and residues 1-1178 of SEQ ID NO:29, which are also identical sequences. The recitation of amino acids 1-1163 of SEQ ID NO:2 has been deleted from claims 114-116. Similarly, the recitation of residues 1-1178 of SEQ ID NO:29 has been deleted from claims 117-119. Accordingly, the objection to claims 114-119, and the objection to claims 123-125, which depend from claims 114-119 should be withdrawn.

2. THE REJECTION UNDER 35 USC § 112, FIRST PARAGRAPH, BASED ON NON-ENABLEMENT SHOULD BE WITHDRAWN

Claims 114, 116-129, and 131-132 are rejected under 35 U.S.C. § 112, first paragraph, because the specification allegedly fails to provide enabling support for these claims. Applicants respectfully disagree as set forth in detail below.

THE LEGAL STANDARD

The test for enablement is whether one reasonably skilled in the art could make or use the invention, without undue experimentation, from the disclosure in the patent specification coupled with information known in the art at the time the patent application was filed. *U.S. v. Telectronics Inc.*, 857 F.2d 778, 8 USPQ2d 1217 (Fed. Cir. 1988). In fact, well known subject matter is preferably omitted. See *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986) ("a patent need not teach, and preferably omits, what is well known in the art."). Further, one skilled in the art is presumed to use the information available to him in attempting to make or use the claimed invention. See *Northern Telecom, Inc. v. Datapoint Corp.*, 908 F.2d 931, 941 (Fed. Cir. 1990) ("A decision on the issue of enablement requires determination of whether a person skilled in the pertinent art, using the knowledge available to such a person and the disclosure in the patent document, could make and use the invention without undue experimentation."). These enablement rules preclude the need for the patent applicant to "set forth every minute detail regarding the invention."

Phillips Petroleum Co. v. United States Steel Corp., 673 F. Supp. 1278, 1291 (D. Del. 1991); see also *DeGeorge v. Bernier*, 768 F.2d 1318, 1323 (Fed. Cir. 1985).

Undue experimentation is experimentation that would require a level of ingenuity beyond what is expected from one of ordinary skill in the field. *Fields v. Conover*, 170 USPQ 276, 279 (CCPA 1971). The factors that can be considered in determining whether an amount of experimentation is undue have been listed in *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Among these factors are: the amount of effort involved, the guidance provided by the specification, the presence of working examples, the amount of pertinent literature and the level of skill in the art. The test for undue experimentation is not merely quantitative, since a considerable amount of experimentation is permissible, so long as it is merely routine. *Id.*

Further, while the predictability of the art can be considered in determining whether an amount of experimentation is undue, mere unpredictability of the result of an experiment is not a consideration. Indeed, the Court of Custom and Patent Appeals has specifically cautioned that the unpredictability of the result of an experiment is not a basis to conclude that the amount of experimentation is undue in *In re Angstadt*, 190 USPQ 214 (CCPA 1976), at 218-219:

> [If to fulfill the requirements of 112, first paragraph, an applicant's] disclosure must provide guidance which will enable one skilled in the art to determine, with reasonable certainty before performing the reaction whether the claimed product will be obtained, ... then all "experimentation" is "undue" since the term "experimentation" implies that the success of the particular activity is uncertain. Such a proposition is contrary to the basic policy of the Patent Act. *Id.* at 219.

Thus, all that is required is a reasonable amount of guidance with respect to the direction of the experimentation; reasonable certainty with regard to the outcome of the experimentation is not required.

In addition, the Patent and Trademark Office bears the initial burden of establishing a *prima facie* case of non-enablement. *In re Marzocchi*, 169 USPQ 367, 369 (C.C.P.A. 1971); M.P.E.P. § 2164.02. A patent applicant's specification which contains a teaching of how to make and use the invention must be taken as enabling unless there is reason to doubt the objective truth of the teachings which must be relied on for enabling support. *Id.*

Further, "if any use is enabled when multiple uses are disclosed, the application is enabling for the claimed invention." M.P.E.P. § 2164.01(c).

THE CLAIMS ARE ENABLED BY THE INSTANT SPECIFICATION

2a) Claims 114, 116-129, and 131-132 are rejected under 35 U.S.C. § 112, first paragraph, because the specification allegedly does not provide enabling support for the use of residues 975-1163 of SEQ ID NO:2, residues 990-1178[6] of SEQ ID NO:29, and SEQ ID NO:32 (rat Nogo C), and homologs thereof. In particular, the Examiner argues that Nogo C's lack of inhibitory activity in the fibroblast spreading assay demonstrates that the Applicants have failed to disclose how to use Nogo C. Applicants respectfully disagree because the specification as originally filed provides sufficient support for the use of Nogo C as an immunogen to make antibodies against Nogo proteins that are active in the fibroblast spreading assay.

The rejection that the claims directed to SEQ ID NO:32 (Nogo C), amino acids 975-1163 of SEQ ID NO:2, and amino acids 990-1178 of SEQ ID NO:29 and homologs thereof are not enabled because these sequences lack inhibitory activity in the fibroblast spreading assay is based on the assumption that the only use disclosed by the specification for Nogo proteins is based on the neurite outgrowth inhibitory activity of certain Nogo proteins. The specification, however, discloses other uses for Nogo proteins such as the use of Nogo proteins as immunogens to generate antibodies against Nogo. Because at least one patentable utility of the claimed amino acid sequences of SEQ ID NO:32 (Nogo C), amino acids 975-1163 of SEQ ID NO:2, and amino acids 990-1178 of SEQ ID NO:29 is enabled, the enablement rejection should be withdrawn. See M.P.E.P. § 2164.01(c).

The generation of antibodies against Nogo proteins is disclosed in section 5.5, beginning at page 28, of the specification as originally filed. In particular, the generation of antibodies against rat Nogo C is disclosed at page 28, line 15. The specification as filed further teaches that these antibodies can be used to localize and measure the activity of Nogo

[6] The recitation of "residues 990-1178" has been replaced in the claims with "the carboxy-terminal 188 amino acids." In order to more easily match Applicants' responses to the corresponding arguments in the Office Action, Applicants refer to "residues 990-1178" in the present response.

proteins of the invention. Nogo A and Nogo C share Exon 3 as shown in Figure 1B. Further, amino acids 975-1163 of SEQ ID NO:2 and amino acids 990-1178 of SEQ ID NO:29 are portions of rat and human Nogo A, respectively. Thus, antibodies generated against SEQ ID NO:32 (Nogo C), amino acids 975-1163 of SEQ ID NO:2, and amino acids 990-1178 of SEQ ID NO:29 are predicted to cross-react with Nogo A. Nogo A's inhibitory activity in the fibroblast spreading assay is demonstrated in the specification as originally filed at page in Table 2 at page 68. Thus, antibodies generated against SEQ ID NO:32 (Nogo C), amino acids 975-1163 of SEQ ID NO:2, and amino acids 990-1178 of SEQ ID NO:29 are predicted to have use in localizing and measuring the activity of Nogo protein that is active in the fibroblast spreading assay.

Because no evidence has been provided in the Office Action as to why the use of SEQ ID NO:32 (Nogo C), amino acids 975-1163 of SEQ ID NO:2, and amino acids 990-1178 of SEQ ID NO:29 as immunogens is not enabled, the Patent and Trademark Office has not met its initial burden of establishing a *prima facie* case of non-enablement.

2b) Claims 123 and 124 are rejected under 35 U.S.C. § 112, first paragraph, because of incorrect dependencies and because the specification allegedly fails to provide sufficient support for how to make other mammalian, and, more specifically, human, Nogo proteins. As shown in more detail below, the specification as originally filed discloses not only different strategies for obtaining other Nogo proteins but also provides working examples to demonstrate the feasibility of these strategies. Additionally, the claims have been amended to remove those dependencies that did not further limit the independent claim.

Claims 123 and 124 have been amended to delete certain dependencies. The dependencies of claim 123 from claims 114, 117, and 120 have been deleted. The dependency of claim 124 from claim 117 has been deleted. The dependencies of claim 124 from claims 114 and 120 have been deleted. Similarly, the dependencies of claim 124 from claims 115 and 116 have been deleted. The dependencies of claims 123 and 124 from 121 have been deleted because claim 121 has been cancelled in the present amendment.

Claims 123 and 124 have been rejected further because the claims from which they depend recite fusion proteins, and such fusion proteins are not mammalian because they are artificially-created. Applicants respectfully disagree because the fusion proteins recited in

claims 115-116[7], *i.e.*, amino acids 1-171 fused to amino acids 975-1163 of SEQ ID NO:2, correspond to the Nogo B isoform of Nogo proteins as discussed in the specification as originally filed at page 11, line 3 and at page 12, lines 19-23, which is naturally occurring in humans (as shown by Prinjha *et al.*, 2000, Nature 403:383-384; attached as Exhibit D).

With regard to the remaining dependencies in claims 123, Applicants respectfully point out that the specification as originally filed provides sufficient enabling support to make and use other mammalian proteins with the amino acid sequence recited in claims 115, 116, 118, 119, or 122, as described below. Similarly, the specification as originally filed provides sufficient enabling support to make and use other human proteins with the amino acid sequence recited in claims 118, 119, or 122, as described below.

The specification provides different strategies that can be employed to isolate other mammalian Nogo proteins without undue experimentation. In addition, the specification provides an adequate number of working examples for the isolation and identification of different mammalian Nogo genes using these different strategies. Similarly, the teachings in the specification can be used to identify and isolate other alleles of human Nogo without undue experimentation. Further, the teachings in the specification can be used in a straightforward manner to identify and isolate isoforms of human Nogo other than human Nogo A (SEQ ID NO:29). For example, human Nogo B is taught in the present specification; at page 12, lines 19-23, it is stated that Nogo B is equivalent to the amino terminal 172 amino acids fused to the carboxy terminal 188 amino acids of Nogo A (SEQ ID NOs:2 and 29). Thus, the skilled artisan can readily derive the amino acid sequence for human Nogo B. The existence of the Nogo B isoform in humans was later confirmed by others (Prinjha *et al.*, 2000, Nature 403:383-384; attached as Exhibit D).

Guidance on how mammalian proteins with the recited amino acid sequences and sequence homologies can be isolated is provided throughout the specification. For example, Section 5.1, beginning at page 12, line 12, describes how genes that encode proteins of certain degrees of sequence homologies can be isolated. In particular, at page 13, line 14 to page 14, line 18, support is provided for hybridization conditions that can be used to obtain nucleic acids that encode the proteins of varying degrees of amino acid sequence homologies. Further, at page 16, lines 5 to 33, the specification enumerates software programs that can be

[7] The recitation of a fusion protein has been deleted from claims 118 and 119.

used by the skilled artisan to identify the claimed proteins or nucleic acids that encode such claimed proteins in a database. The specification teaches at page 17, line 15, that about 180 amino acids at the carboxy-terminus of Nogo A (SEQ ID NO:2) are conserved among different species. In particular, the evolutionary conservation of two hydrophobic regions in the carboxy-terminus of Nogo protein is demonstrated in Figure 3B. It is commonly known to the skilled artisan that regions of a gene that encode a conserved domain are preferably used to identify homologs of the gene in other species. Clearly, if a region of a protein is conserved between two species, such as rat and bovine as shown in Figure 3B, this region is most likely also conserved in homologs of the protein in other species. Also, the specification clearly teaches that primers to Nogo segments conserved between species are preferably used to isolate Nogo genes (see, *e.g.*, page 18, lines 13-15, of the specification). At page 18, lines 11-31, the specification describes how polymerase chain reaction ("PCR") can be used to identify proteins that fall within the scope of the claimed proteins. As taught in the specification, primers for the PCR reaction preferably are designed based on the nucleic acid sequence that encodes a conserved region of the protein, such as the conserved carboxy-terminal 180 amino acids of Nogo A. Additionally, at page 18, lines 5-10, the specification describes how expression libraries can be used to identify Nogo homologs. Antibodies that can be used to identify homologs of Nogo in an expression library are also provided by the present specification, see, *e.g.*, at page 28, line 1 to page 29, line 32. Strategies for cloning genes encoding the claimed proteins from genomic DNA are described, *e.g.*, at pages 18-21.

Moreover, the specification provides several working examples describing the isolation and characterization of the claimed proteins using different methods. In Example 6.2.1, beginning at page 62, the isolation of a cDNA encoding a Nogo protein is described. Briefly, a portion of the biochemically purified bovine Nogo protein was microsequenced and the amino acid sequence information was used to design degenerate oligonucleotides. A screen of a bovine white matter cDNA library using these oligonucleotides as probes yielded several clones. DNA from the longest clone was used to synthesize probes for screening a rat cDNA library. This screen yielded the rat Nogo A, B, and C transcripts. Thus, the isolation of the bovine and rat Nogo genes provides a working example for the use of nucleic acid hybridization in obtaining Nogo genes from different mammalian species. The identification of human Nogo is described in section 7, page 69, lines 1-20. The human Nogo sequence was identified using the rat sequence as a frame of reference for the alignment and assembly

of human EST sequences. The identification of human Nogo provides a working example for using information in sequence databases to obtain Nogo genes.

Because of the conserved structure and function of Nogo across species, the isolation and/or identification of Nogo genes in other mammalian species would not require undue experimentation. The cross-species experiments described in the specification also demonstrate the conservation of Nogo structure and function across species. For example, at page 65, lines 15-16, it is described that bovine Nogo can inhibit the neurite outgrowth of NIH 3T3 cells, a mouse cell line. This concept is also supported by the observation that antibodies against the bovine Nogo protein promote neurite outgrowth of chicken dorsal root ganglia (see specification at page 65, lines 16-20).

Regions of the Nogo protein that confer inhibitory activity, *e.g.*, regions that inhibit spreading of fibroblasts, are identified, as described in section 6.2.7 of the specification at page 67, line 18, to page 68, line 33. The skilled artisan would know that if the sequence of the major inhibitory domain (specification at page 68, lines 28-30) is conserved, the inhibitory activity will also very likely be conserved. It is commonly known to the skilled artisan that the amino acid sequence of a functional region of a protein is predicted to be conserved across species if the function of that region is maintained in different homologs of the protein. Thus, it would be commonly known to the skilled artisan preferably to use the nucleic acid sequence that encodes the major inhibitory domain of Nogo to isolate homologs of Nogo. Nucleic acid sequences that encode the major inhibitory domain of Nogo can be used (i) to design PCR primers for the amplification of cDNAs encoding Nogo homologs from a cDNA library; (ii) to design RT-PCR primers for the amplification of cDNAs encoding Nogo homologs from an RNA preparation; or (iii) to design probes for the screening of a cDNA library by hybridization; or the sequence information can be used to query electronic databases to identify sequences of Nogo homologs using homology searches. Applicants' examples show that these techniques can be successfully performed without undue experimentation.

2c) Claim 127 is rejected under 35 U.S.C. § 112, first paragraph, because, in the absence of the recitation of a washing step, the claims allegedly read on an infinite number of DNA sequences. Without making any admission and solely to expedite the prosecution of this application, Applicants have amended the claim to recite a washing step for high stringency hybridization, thus obviating the rejection.

2d) Claims 129 and 131 are rejected under 35 U.S.C. § 112, first paragraph, because the specification allegedly fails to provide sufficient enabling support for transgenic animals that comprise vectors encoding Nogo proteins. Without making any admission and solely to expedite the prosecution of this application, Applicants have amended the claim to clarify that the claimed host cells reside *ex vivo*, thus obviating the rejection.

For the reasons set forth above the rejections of claims 114, 116-129, and 131-132 under 35 U.S.C. § 112, first paragraph, for lack of enablement, should be withdrawn.

3. THE REJECTION UNDER 35 U.S.C. § 112 BASED ON LACK OF WRITTEN DESCRIPTION SHOULD BE WITHDRAWN

Claims 115-116, 118-119, and 121-132 are rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the written description requirement. Applicants respectfully disagree as set forth in detail below.

THE LEGAL STANDARD

The test for sufficiency of written description is whether the disclosure of the application 'reasonably conveys to the artisan that the inventor had possession' of the claimed subject matter. *In re Kaslow*, 707 F.2d 1366, 1375, 217 U.S.P.Q. (BNA) 1089, 1096 (Fed. Cir. 1983); accord *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563; *see also, Ralston Purina Co. v. Far-Mar-Co, Inc.*, 772 F.2d 1570, 1575, 227 U.S.P.Q. (BNA) 177, 179 (Fed. Cir. 1985). The Court of Appeals for the Federal Circuit has repeatedly considered the written description requirement and consistently found that exacting detail is not necessary to meet the requirement:

> If a person of ordinary skill in the art would have understood the inventor to have been in possession of the claimed invention at the time of filing, even if [not] every nuance of the claims is explicitly described in the specification, the adequate written description requirement is met. *In re Alton*, 76 F.3d 1168, 37 USPQ2d 1578 (Fed. Cir. 1996).

The criteria for determining sufficiency of written description set forth in Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112 ¶ 1, "Written Description

Requirement" ("the Guidelines") (published in the January 5, 2001 Federal Register at Volume 66, Number 4, p. 1099-1111), specifies that:

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice (see (1)(a) above), reduction to drawings (see (1) (b) above), or by disclosure of relevant, identifying characteristics, *i.e.*, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus (see (1)(c), above). *Id.* at p. 1106, column 3, *l.* 13-29.

Where the specification discloses any relevant identifying characteristics, *i.e.*, physical, chemical and/or functional characteristics sufficient to allow a skilled artisan to recognize the applicant was in possession of the claimed invention, a rejection for lack of written description under Section 112, first paragraph, is misplaced. *Id.*

Furthermore, in accordance with the Guidelines, what is conventional or well known to one of skill in the art need not be disclosed in detail (*Id.* at p. 1105, column 3, *ll.* 39-41), and, where the level of knowledge and skill in the art is high, a written description question should not be raised. *Id.* at p. 1106, column 1, *ll.* 34-36. See also *Capon v. Eshhar*, 418 F.3d 1349, at 1357 (Fed. Cir. 2005).

THE INSTANT SPECIFICATION PROVIDES SUFFICIENT WRITTEN DESCRIPTION FOR THE CLAIMS

3a) Claims 115-116, 118-119, and 121-122 are rejected under 35 U.S.C. § 112, first paragraph, because the specification allegedly fails to provide sufficient written description support for proteins with 90% and 95% sequence identity to the recited sequences. In particular, it is alleged that Applicants have failed to provide common structural elements that are present in all members of the claimed genera.

Applicants respectfully disagree because the specification discloses, *inter alia*, functional characteristics, which are either known to correlate with structural characteristics or disclosed to correlate with structural characteristics. In particular, the specification discloses that the proteins have (a) neurite outgrowth inhibitory activity; and/or (b) immunogenicity/antigenicity. The common structural elements that correlate with neurite outgrowth inhibitory activity are explicitly taught in the specification, the characteristics of

common structural elements that correlate with immunogenicity/antigenicity are known to the skilled artisan and are taught in the specification (see page 27, lines 21-24; and page 28, lines 8-10) and thus can be readily identified by the skilled artisan.

Regions of the Nogo protein that confer inhibitory activity, *e.g.*, regions that inhibit spreading of fibroblasts, are identified, as described in section 6.2.7 of the specification at page 67, line 18, to page 68, line 33. It is commonly known to the skilled artisan that the amino acid sequence of a functional region of a protein is likely conserved across species if the function of that region is maintained in different homologs of the protein. Clearly, the amino acid sequence of a functional region of a protein is also maintained among various alleles of the gene encoding the protein. Thus, one common structural element that has been taught in the specification is the domain of Nogo that is required for Nogo inhibitory activity.

The specification further teaches that the claimed Nogo proteins are immunogenic, and thus, for example, can be used to prepare antibodies. As is known in the art, regions of proteins that are relatively hydrophilic are predicted to be immunogenic (see Hopp and Woods, discussed below). At page 27, lines 21-24, of the specification, it is disclosed that hydrophilicity analyses can be performed on the Nogo protein sequences. In particular, Hopp and Woods, 1981, PNAS 78:3824 ("Hopp and Woods," attached hereto as Exhibit E) is cited. Hopp and Woods describes how such a hydrophilicity analysis can be used to predict antigenic determinants in a protein; Hopp and Woods states that "[t]he point of highest local average hydrophilicity is invariably located in, or immediately adjacent to, an antigenic determinant" (see the Abstract). Further, at page 28, lines 8-10, of the present specification, it is stated that fragments of a Nogo protein that have been identified as being hydrophilic can be used as immunogens for antibody production.

Accordingly, the skilled artisan can readily carry out a hydrophilicity analysis as taught in the specification to predict immunogenic portions of the claimed proteins and fragments. Indeed, a hydrophilicity analysis by way of example, has been performed essentially according to the method of Hopp and Woods for the claimed amino acid sequences as set forth in Exhibit C. The hydrophilicity analyses were performed on July 6, 2005, July 8, 2005, and July 11, 2005, respectively, using an online service of the Expert Protein Analysis System proteomics server of the Swiss Institute of Bioinformatics (SIB) (URL: http://us.expasy.org/tools/protscale.html). For the online analysis, Hopp and Woods' amino acid scale and a window size of seven amino acids were selected. Print-outs of the

hydrophilicity analyses are attached as Exhibit C. Points of highest local average hydrophilicity can be seen throughout the amino acid sequence for all sequences as set forth in the Summary Of Nogo Hydrophilicity Analysis (Exhibit C), indicating that antigenic determinant(s), predicted to confer immunogenicity, are present in claimed proteins/fragments. Thus, the antigenic determinants of the claimed Nogo proteins are additional common structural elements that are taught in the specification.

With regard to the rejections of claims 121 and 122, Applicants point out that claim 121 has been cancelled and claim 122 has been amended to recite a sequence homology of 97% and that the protein can be bound by an antibody that also binds to a protein of claim 114, 115, or 116.

3b) Claims 123 and 124 are rejected under 35 U.S.C. § 112, first paragraph, because of inaccurate dependencies and because the specification allegedly fails to provide sufficient written description support for other mammalian and human Nogo proteins. Applicants point out that the specification as originally filed shows that Applicants were in possession of a representative number of species within the claimed genera. Further, the claims have been amended to remove certain dependencies.

The deletion of certain dependencies in claims 123 and 124 has been discussed in section 2b above. The specification as filed provides sufficient evidence that Applicants were in possession of the claimed genera as set forth above in section 3a. Further, the fusion protein and the fragments recited in the claims correspond to naturally occurring isoforms of Nogo, namely Nogo B and Nogo C. The existence of all three isoforms of Nogo in humans has been confirmed (see, Exhibit D). Thus, the specification provides a representative number of species, namely human Nogo A, B, and C as well as rat Nogo A, B, and C to support the claimed genera of human and mammalian proteins, respectively.

3c) Claim 127 is rejected under 35 U.S.C. § 112, first paragraph, because, in the absence of the recitation of a washing step, the claims allegedly read on an infinite number of DNA sequences. Without making any admission and solely to expedite the prosecution of this application, Applicants have amended the claim to recite a washing step for high stringency hybridization, thus obviating the rejection.

3d) Claims 117-119 are rejected under 35 U.S.C. § 112, first paragraph, because the specification allegedly lacks support for the recitation of amino acids 990-1178 of SEQ ID

NO:29. Applicants respectfully point out that the claims 118 and 119 have been amended to delete the recitation of amino acids 990-1178, and claim 117 has been amended to recite "the carboxy-terminal 188 amino acids of SEQ ID NO:29." Support for this amendment can be found in the specification as filed at page 12, line 21 and line 26. Thus, the rejection has been obviated.

3e) Claims 121 and 122 are rejected under 35 U.S.C. § 112, first paragraph, because the specification allegedly lacks written description support for homologs of SEQ ID NO:32 (Nogo C) that have Nogo activity. Applicants respectfully point out that claim 121 has been cancelled, and claim 122 has been amended to recite that the claimed protein has Nogo protein antigenicity. The specification as originally filed discloses at page 11, lines 22-30 that one functional activity of the proteins of the invention is their antigenicity, *i.e.*, the ability to bind to an anti-Nogo antibody. As discussed in section **3a**, SEQ ID NO:32 (Nogo C) is predicted to be immunogenic/antigenic according to a hydrophilicity analysis (Exhibit C). Thus, the claimed proteins have an activity that was disclosed in the specification as originally filed.

3f) Claims 123 and 124 are rejected under 35 U.S.C. § 112, first paragraph, because the specification as originally filed allegedly lacks written description support for mammalian proteins with Nogo activity other than rat and human Nogo proteins since such other proteins are not contemplated by the specification. Applicants respectfully disagree because the specification as originally filed clearly conveys that Nogo proteins other than rat or human are within the scope of the invention.

The specification names several exemplary mammalian species other than rat or human whose Nogo proteins are considered to be within the scope of the invention. At page 10, lines 35-36, it is stated that the Nogo genes and proteins are from mammals. Further, at page 18, lines 34 to page 19, line 1, it is stated that Nogo genes can be isolated from mammalian sources. At page 30, lines 2-5, it is stated that, among others, mouse, rat, pig, cow, dog, monkey, and human Nogo proteins are within the scope of the invention. At page 55, lines 14-26, the generation of Nogo "knockout" animals is discussed. Exemplary animals are listed at page 55, line 25, and include mice, hamsters, sheep, pigs, and cattle. It is stated that these recombinant animals can be used as animal models for diseases and disorders involving neurite extension, growth, and regeneration (page 55, lines 14-15). Thus, the specification as originally filed demonstrates that Applicants considered non-rat and non-

human Nogo proteins with Nogo activity as defined at page 11, lines 20-30, to be within the scope of the invention.

As discussed above in section 3a, the specification discloses several functional characteristics of Nogo proteins, *i.e.*, neurite outgrowth inhibitory activity and immunogenicity/antigenicity. These functional characteristics have been disclosed to, or are known to, correlate with certain structural features. The domains supporting neurite outgrowth inhibitory activity are disclosed in the specification (page 67, line 18, to page 68, line 33), and the regions conferring immunogenicity/antigenicity are known to be relatively hydrophilic and can readily be deduced by the skilled artisan using a hydrophilicity analysis (see Exhibit C). Thus, the claimed genera of mammalian and human Nogo proteins, respectively, are supported by sufficient written description in the specification.

Further, the specification discloses a representative number of species within the claimed genera. As discussed above in section 3b, the specification as originally filed provides the sequences of three human Nogo proteins with Nogo activity (at least antigenicity/immunogenicity), namely Nogo B and Nogo C, as well as Nogo A (SEQ ID NO:29). In addition to the sequences of rat Nogo A (SEQ ID NO:2), the sequences of rat Nogo B and rat Nogo C are disclosed in the specification.

For the reasons set forth above the rejections of claim 115-119, 121-124, and 127, under 35 U.S.C. § 112, first paragraph, for lack of written description, should be withdrawn.

4. THE REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH, SHOULD BE WITHDRAWN

Claims 115-116, 118-119, 123-125, and 127 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

4a) Claims 115 and 116 are rejected as allegedly being indefinite. In particular, it is argued that in the case of the recitation of sequence identities to amino acids 1-171 fused to amino acids 975-1163 of SEQ ID NO:2 and 1-172 fused to 990-1178 of SEQ ID NO:29, respectively, it is not clear whether the recited sequence identity relates only to the first segment of the fusion or to the entire fused sequences. Applicants have amended the claim to clarify that the recited sequence identities relate to the entire fused sequences.

4b) Claims 123 and 124 are rejected as allegedly being indefinite. In particular, it is argued that the fusion proteins that are recited in the claims from which 123 and 124, respectively, depend are neither human or mammalian. First, claims 123 and 124 as amended properly further limit the claims from which they depend. Thus, any Nogo protein claimed in a claim from which 123 and 124 depend that is not mammalian or not human, would simply not be encompassed by claim 123 or 124, respectively. Second, the fused sequences recited in claim 123 via its dependency from claims 115 and 116 correspond to the amino acid sequence of Nogo B as discussed above (see, page 12, lines 19-22, of the specification as filed). Thus, the recited fused sequences are naturally occurring, *i.e.*, they are human or mammalian, respectively. The existence of rat Nogo B has been demonstrated in the instant specification (see page 62, lines 22-24); the existence of human Nogo B subsequently has been verified by others (see Exhibit D).

4c) Claim 127 is rejected as allegedly being indefinite because it recites the trademark Ficoll®. The standard under M.P.E.P. § 2173.05(u) as to whether or not a trademark can properly be recited in a claim is whether or not "is used to identify the source of goods, and not the goods themselves." Applicants respectfully assert that the presence of Ficoll® in the claim is proper since it is used as a source-identifier.

Ficoll® is routinely used in hybridization protocols. The common recognition in the art of the trademark Ficoll® as a source-identifier for a chemical that can be obtained from Pharmacia is demonstrated by the fact that a leading laboratory manual such as Sambrook, Fritsch, and Maniatis, Cold Spring Harbor Laboratory Press, 1989, uses the trademark instead of a chemical name (see Exhibit A; "Maniatis"). Maniatis specifies that Ficoll® can be obtained from Pharmacia, thus demonstrating that Ficoll® is used as a source-identifier.[8]

The use of the trademark Ficoll® in claim 127 is proper because it is not a use of a trademark that is proscribed in M.P.E.P. § 2173.05(u). This section of the M.P.E.P. states that the trademark should not be used to describe or identify the goods when such a use would (i) render the claim indefinite and (ii) constitute an improper use of the trademark.

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[8] The general acceptance of the trademark Ficoll® as a claim term is also evidenced by the fact that numerous U.S. patents that recite Ficoll in their claims have been issued. According to a search conducted on September 20, 2005 at the PTO's website (www.pto.gov), for the term "Ficoll" in the claims, using the PTO's online search software and the PTO's online patent full-text database, between 1976 and September 20, 2005, 140 U.S. Patents have been issued with the recitation of FICOLL in the claims.

Such an improper use would be for example to recite "Xerox® machine" to describe any copy machine. The recitation of Ficoll® in the present claim, however, is used to identify a composition sold by Pharmacia. Thus, the use of Ficoll® in the present claim is a proper use of a trademark as a source-identifier and does not render the claim indefinite.

5. THE REJECTIONS UNDER 35 USC §§ 102(b) AND (e) SHOULD BE WITHDRAWN

THE LEGAL STANDARD

Anticipation requires that the same invention, including each element and limitation of the claims, was known or used by others before it was invented by the patentee. *Hoover Group, Inc. v. Custom Metalcraft, Inc.*, 66 F. 3d 299, 302 (Fed. Cir. 1995). An anticipating reference must describe and enable the claimed invention, including all the claim limitations, with sufficient clarity and detail to establish that the subject matter already existed in the prior art and that its existence was recognized by persons of ordinary skill in the field of the invention. *In re Spada*, 911 F.2d 705 (Fed. Cir. 1990); *Crown Operations International, Ltd. v. Solutia Inc.*, 289 F.3d 1367, 1375 (Fed. Cir. 2002).

The standard for an anticipatory reference is set forth in *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987): "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *See also Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236 (Fed. Cir. 1989)(holding that "[t]he identical invention must be shown in as complete detail as is contained in the . . . claim"). Further, the anticipating reference must disclose every element of the challenged claim and enable one skilled in the art to make the anticipating subject matter. *PPG Industries, Inc. v. Guardian Industries Corp.* 75 F. 3d 1558 (Fed. Cir. 1996).

THE EFFECTIVE FILING DATE OF ALL CLAIMS IS NOVEMBER 6, 1998

5a) The Examiner has determined that the effective filing date for claims 117-119 and 123-132 is September 24, 2001 and not the filing date of the provisional application no. 60/107,446 filed November 6, 1998 (the "Priority Application") because the Priority Application allegedly lacks support for the recitation of the protein fragment of amino acids

990-1178. Applicants respectfully point out that the claims 118 and 119 have been amended to delete the recitation of amino acids 990-1178, and claim 117 has been amended to recite "the carboxy-terminal 188 amino acids of SEQ ID NO:29." Support for this amendment can be found in the Priority Application at page 13, lines 15-21. Further written description and enabling support under Section 112 for claims 117 to 119 can be found at page 11, lines 28-29; Figure 13; page 13, lines 15-28; page 18, lines 18-25; page 32, line 31 to page 33, line 2; Figure 14; and page 18, lines 18-25 of the Priority Application. Support for the dependent claim 123-132 can be found in the Priority Application as set forth in the chart below:

Claim	Support in the Priority Application
123-124	page 22, line 12
125	page 11, lines 28-29
126	page 13, line 8 to page 14, line 10
127	page 15, lines 16-29
128	page 24, lines 22-30; page 26, lines 5-10
129	page 25, lines 19-25; page 51, lines 8-14
130	page 97, lines 13-14
131	page 97, lines 15-16
132	page 4, lines 20-22

Accordingly, the effective filing date for claims 117-119 and 123-132 is November 6, 1998.

5b-1 STRATAGENE DOES NOT ANTICIPATE CLAIM 127

Claim 127 is rejected under 35 U.S.C. §102(b) over the publication of random primers in the 1991 Stratagene catalog, page 66 ("Stratagene"). In particular, it is argued that random primers would remain hybridized to the target sequence under the conditions recited in the claims because the claim language fails to set forth washing conditions. Without making any admission, and solely to expedite the prosecution, Applicants have amended claim 127 to recite stringent washing conditions. Accordingly, the rejection over Stratagene should be withdrawn.

5b-2 BANDMAN DOES NOT ANTICIPATE CLAIMS 115-116 AND 125-132

Claims 115-116 and 125-132 are rejected under 35 U.S.C. § 102(e) over U.S. Patent 5,858,708 to Bandman et al. ("Bandman"). In particular, it is argued that amino acid residues 12-199 of Bandman's SEQ ID NO:1 are 97.7% identical to amino acid residues 976-1163 of SEQ ID NO:2 in the present application. Claim 116 has been amended to delete the recitation of an amino acid sequence with 95% or greater sequence identity with amino acids 975-1163 of SEQ ID NO:2.

Bandman does not disclose an amino acid sequence in which more than 90% (claim 115) or 95% (claim 116) of the amino acid residues are identical to the amino acid residues of the instant application's SEQ ID NO:2 (rat Nogo A) in an alignment. Nor does Bandman disclose an amino acid sequence in which more than 90% (claim 115) or 95% (claim 116) amino acid residues are identical to the amino acid residues of an aligned amino acid sequence in which amino acids 1-171 are fused to amino acids 975-1163 of SEQ ID NO:2 (rat Nogo B). Rat Nogo A is 1163 amino acids long and rat Nogo B is 359 amino acids long; in contrast, Bandman's SEQ ID NO:1 is 199 amino acids long. Thus, it is not possible that 90% or even 95% of the amino acid residues of rat Nogo A or rat Nogo B are identical to Bandman's SEQ ID NO:1 because Bandman's SEQ ID NO:1 has only 17% of the amino acids of rat Nogo A and only 55% of the amino acids of rat Nogo B.

It is further argued that Bandman's SEQ ID NO:2, which encodes Bandman's SEQ ID NO:1, anticipates claims 126 and 127. As discussed above, Bandman's SEQ ID NO:1 represents only 17% and 55%, respectively, of the amino acid sequence of rat Nogo A and rat Nogo B. Accordingly, Bandman's SEQ ID NO:2 does not encode one of the claimed homologs of rat Nogo A or rat Nogo B and, therefore, does not anticipate claim 126.

Claim 127 has been amended to recite that the nucleotide sequence of claim 126 encodes a protein with inhibitory activity in an NIH 3T3 fibroblast spreading assay. As set forth in the Office Action, Bandman's SEQ ID NO:1, which is encoded by Bandman's SEQ ID NO:2, is homologous to amino acid residues 976-1163 of Applicants' SEQ ID NO:2 (Nogo C). Nogo C, however, lacks inhibitory activity in an NIH 3T3 fibroblast spreading assay as shown in the present specification at page 68, Table 2. Thus, Bandman's SEQ ID NO:2 does not fall within the scope of claim 127 and therefore does not anticipate the claim.

Thus, the rejection of claims 115, 116, 126, and 127 over Bandman should be withdrawn. Similarly, the rejection of dependent claims 125 and 128-132 should likewise be withdrawn.

5b-3 BANDMAN DOES NOT ANTICIPATE CLAIMS 118-119 AND 125-132

Claims 118-119 and 125-132 are rejected under 35 U.S.C. § 102(e)[9] over Bandman. In particular, it is argued that amino acid residues 12-199 of Bandman's SEQ ID NO:1 are 99.6% identical to amino acid residues 990-1178 of SEQ ID NO:29 in the present application. Claim 119 has been amended to delete the recitation of an amino acid sequence with 95% or greater sequence identity with amino acids 990-1178 of SEQ ID NO:29.

Bandman does not disclose an amino acid sequence in which at least 90% (claim 118) or 95% (claim 119) of the amino acid residues are identical to the amino acid residues of the instant application's SEQ ID NO:29 (human Nogo A) in an alignment. Further, Bandman does not disclose an amino acid sequence in which at least 90% (claim 118) or 95% (claim 119) of the amino acid residues are identical to the amino acid residues of an aligned amino acid sequence in which amino acids 1-172 are fused to amino acids 990-1178 of SEQ ID NO:2 (human Nogo B). Human Nogo A is 1178 amino acids long and human Nogo B is 360 amino acids long; in contrast, Bandman's SEQ ID NO:1 is 199 amino acids long. Thus, it is not possible that at least 90% (claim 118) or even 95% (claim 119) of the amino acid residues of rat Nogo A or rat Nogo B are identical to Bandman's SEQ ID NO:1 because Bandman's SEQ ID NO:1 has only 17% of the amino acids of human Nogo A and only 55% of the amino acids of human Nogo B.

It is further argued that Bandman's SEQ ID NO:2, which encodes Bandman's SEQ ID NO:1, anticipates claims 126 and 127. As discussed above, Bandman's SEQ ID NO:1 represents only 17% and 55%, respectively, of the amino acid sequence of human Nogo A and human Nogo B. Accordingly, Bandman's SEQ ID NO:2 does not encode one of the homologs of human Nogo A or human Nogo B and, therefore, does not anticipate claim 126.

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[9] In the Office Action, it is stated that the rejection is made under 35 U.S.C. § 102(b). However, as discussed above in Section 5a, all claims are entitled to an effective filing date of November 6, 1998. Thus, Bandman, which issued on January 12, 1999, cannot be prior art under 35 U.S.C. § 102(b). Accordingly, Applicants discuss the rejection as if it had been made under 35 U.S.C. § 102(e).

Claim 127 has been amended to recite that the nucleotide sequence of claim 126 encodes a protein with inhibitory activity in an NIH 3T3 fibroblast spreading assay. As set forth in the Office Action, Bandman's SEQ ID NO:1, which is encoded by Bandman's SEQ ID NO:2, is homologous to amino acid residues 976-1163 of Applicants' SEQ ID NO:2 (Nogo C). Nogo C lacks inhibitory activity in an NIH 3T3 fibroblast spreading assay as shown in the present specification at page 68, Table 2. Thus, Bandman's SEQ ID NO:2 does not fall within the scope of claim 127 and therefore does not anticipate the claim.

Thus, the rejections of claims 115, 116, 126, and 127 over Bandman should be withdrawn. Similarly, the rejection of dependent claims 125 and 128-132 should likewise be withdrawn.

5b-4 MICHALOVICH IS NOT PRIOR ART AND THUS CANNOT ANTICIPATE CLAIMS 115-119, 123, AND 125-132

Claims 115-119, 123, and 125-132 are rejected under 35 U.S.C. 102(e) as being allegedly anticipated by U.S. Patent Application Publication 2002/0010324 to Michalovich ("Michalovich").

Michalovich is a continuation application of U.S. Application serial no. 09/359,208 filed July 22, 1999. Michalovich further claims benefit of priority of two foreign applications, which were filed on July 22, 1998 and July 19, 1999, respectively. "Foreign applications' filing dates that are claimed . . . in applications, which have been published as U.S. or WIPO application publications or patented in the U.S., may not be used as 35 U.S.C. 102(e) dates for prior art purposes." M.P.E.P. § 2136.03(I). Thus, Michalovich is available as a reference under 35 U.S.C. 102(e) only as of July 22, 1999. Applicants' priority date of November 6, 1998 predates Michalovich. Thus, Michalovich is not available as prior art under 35 U.S.C. 102(e) against the presently pending claims and the rejection over Michalovich should be withdrawn.

5b-5 EISENBACH-SCHWARTZ IS NOT PRIOR ART AND THUS CANNOT ANTICIPATE CLAIMS 117-119 AND 123-127

Claims 117-119 and 123-127 are rejected under 35 U.S.C. § 102(e) as allegedly anticipated by U.S. Patent Application Publication 2002/0072493 by Eisenbach-Schwartz et al. ("Eisenbach-Schwartz").

The Examiner and Applicants agree that Eisenbach-Schwartz' effective filing date is June 28, 2001. However, the Examiner contends that claims 117-119 and 123-132 are only entitled to the September 24, 2001 filing date of the present application and that Eisenbach-Schwartz is therefore prior art against these claims. Applicants respectfully disagree because, as set forth in Section 5a above, claims 117-119 and 123-132 as presently amended are supported in the priority application and thus are entitled to an effective filing date of November 6, 1998. Because Eisenbach-Schwartz therefore is not available as prior art against the presently pending claims, the rejection over Eisenbach-Schwartz should be withdrawn.

5b-6 CAO DOES NOT ANTICIPATE CLAIMS 118-119 AND 123-125

Claims 118-119 and 123-125 are rejected under 35 U.S.C. § 102(e) over U.S. Patent Application Publication 2002/0034800 by Cao et al. ("Cao") allegedly because amino acid residues 1-373 of Cao's SEQ ID NO:6 are 99.1% identical to amino acid residues 1-172 fused to 990-1178 of SEQ ID NO:29 of the present application. Claims 118 and 119 have been amended to delete the recitation of "an amino acid sequence which has 90% (or 95%, respectively) or greater sequence identity with amino acids 1-172 fused to amino acids 990-1178 of SEQ ID NO: 29." Accordingly, the rejection of claims 118 and 119 over Cao should be withdrawn. Similarly, the rejection of claims 123 to 125, which depend from claims 118 and 119, should be withdrawn.

5b-7 AA986233 DOES NOT ANTICIPATE CLAIMS 126-128

Claims 126-128 are rejected under 35 U.S.C. § 102(b) over GenBank® entry at accession number AA986233 ("AA986233") because allegedly AA986233 encodes a protein that is 90.14% identical to SEQ ID NO:32. Isolated proteins consisting of the amino acid sequence of SEQ ID NO:32 or homologs thereof are claimed in claims 120 and 122 from which claims 126-128 depend. Applicants point out that a Substitute Sequence Listing with a corrected SEQ ID NO:32 has been submitted concurrently herewith. An alignment of the

protein encoded by AA986233 and corrected SEQ ID NO:32 reveals a 95% identity in aligned amino acid residues between the two proteins (see Exhibit B, attached hereto). The alignment between these two sequences was conducted on August 24, 2005 using the online "Blast 2 Sequences" software at the website of the National Center for Biotechnology Information (http://www.ncbi.nlm.nih.gov/blast/bl2seq/wblast2.cgi). Default settings were used for the alignment; these settings are also indicated in Exhibit B. Claim 121 has been cancelled and claim 122 has been amended to recite at least 97% amino acid sequence identity between the claimed protein and SEQ ID NO:32. Thus, the rejection of claims 126-128 over AA986233 has been obviated and should be withdrawn.

5b-8 AF132047 AND AB015639 ARE NOT PRIOR ART AND CANNOT ANTICIPATE CLAIMS 126-127

GenBank® entries at accession numbers AF132047 and AB015639 ("AF132047" and "AB015639")

The publication dates of AF132047 and AB015639 are May 18, 1999 and September 3, 1999, respectively. Claims 126 and 127 are entitled to the priority date of November 6, 1998 as discussed above under Section 5a. Thus, because the effective filing date to which the rejected claims are entitled predates the publication dates of AF132047 and AB015639, neither one of these GenBank® entries is prior art against the pending claims.

6. THE REJECTION UNDER 35 USC § 103 SHOULD BE WITHDRAWN

Claims 128-132 are rejected under 35 U.S.C. § 103(a) over AA986233 or AF132047 or AB015639 or Eisenbach-Schwartz, each in view of Schendel 1998 (Current Protocols in Molecular Biology 16.1.1 – 16.1.3; "Schendel").

THE LEGAL STANDARD

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the prior art references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation

of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. M.P.E.P. 2143.

A finding of obviousness under 35 U.S.C. § 103(a) requires a determination that the differences between the claimed subject matter and the prior art are such that the subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. *Graham v. Deere*, 383, U.S. 1 (1956). The relevant inquiry is whether the prior art suggests the invention and whether the prior art provides one of ordinary skill in the art with a reasonable expectation of success. Both the suggestion and the reasonable expectation of success must be found in the prior art. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

AF132047, AB015639, AND EISENBACH-SCHWARTZ ARE NOT PRIOR ART

As discussed above, AF132047, AB015639, and Eisenbach-Schwartz are not prior art against the pending claims. Thus, the obviousness rejection over AF132047, AB015639, or Eisenbach-Schwartz, each in view of Schendel should be withdrawn.

AA986233 IN VIEW OF SCHENDEL DOES NOT MAKE CLAIMS 128-132 OBVIOUS

Even assuming *arguendo*, there is a motivation and an expectation of success in the prior art to combine AA986233 with Schendel, this combination does not teach all elements of claim 128 because AA986233 does not encode a protein of any of the claims from which claim 128 depends as discussed above in section 5b-7. Schendel, which provides general teachings for protein expression, does not remedy the deficiency in the teachings of AA986233. Accordingly, the rejection over AA986233 in view of Schendel should be withdrawn.

CONCLUSION

Applicants respectfully request that the present remarks and amendments be entered and made of record in the instant application. An allowance of the application is earnestly

requested. If any issues remain in connection herewith, the Examiner is respectfully invited to telephone the undersigned to discuss the same.

Respectfully submitted,

Date: December 28, 2005

Adriane M. Antler 32,605
Adriane M. Antler (Reg. No.)

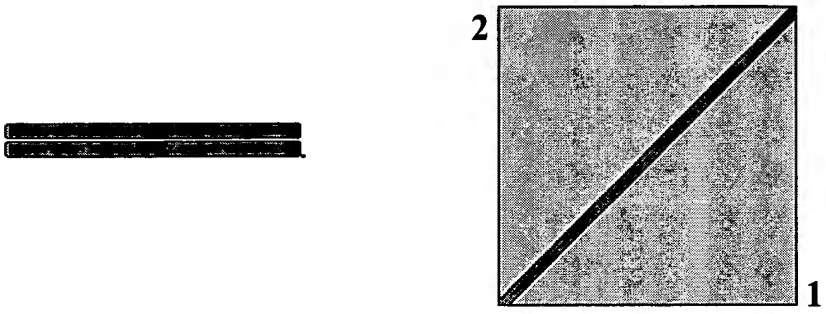
JONES DAY
222 East 41st Street
New York, New York 10017
Telephone Number: 212-326-3939
Fax No.: 212-755-7306

Blast 2 Sequences results

BLAST 2 SEQUENCES RESULTS VERSION BLASTP 2.2.10 [Oct-19-2004]

Matrix BLOSUM62 gap open: 11 gap extension: 1
x_dropoff: 50 expect: 10.000 wordsize: 3 Filter ☐ Align

Sequence 1 lcl|seq id no 32 **Length** 199 (1 .. 199)
Sequence 2 lcl|frame no 2 of translated aa986233 **Length** 200 (1 .. 200)



NOTE:The statistics (bitscore and expect value) is calculated based on the size of nr database

```
Score =  368 bits (945), Expect = e-101
Identities = 190/199 (95%), Positives = 193/199 (96%)

Query: 1   MDGQKKHWKDKVVDLLYWRDIKKTGVVFGASLFLLLSLTVFSIVSVTAYIALALLSVTIS 60
           MD QKK WKDKVVDLLYWRDIKKTGVVFGASLFLLLSLTVFSIVSVTAYIALALLSVTIS
Sbjct: 1   MDDQKKRWKDKVVDLLYWRDIKKTGVVFGASLFLLLSLTVFSIVSVTAYIALALLSVTIS 60

Query: 61  FRIYKGVIQAIQKSDEGHPFRAYLESEVAISEELVQKYSNSALGHVNSTIKELRRLFLVD 120
           FRIYKGVIQAIQKSDEGHPFRAYLESEVAISEELVQKYSNSALGHVNSTIKELRRLFLVD
Sbjct: 61  FRIYKGVIQAIQKSDEGHPFRAYLESEVAISEELVQKYSNSALGHVNSTIKELRRLFLVD 120

Query: 121 DLVDSLKFAVLMWVFTYVGALFNGLTLLILALISLFSIPVIYERHQVQIDHYLGLANKSV 180
           DLVDSLKFAVLMWVFTYVGALFNGLTLLI ALISLFSIPVIYERHQ QIDHYLGLANKSV
Sbjct: 121 DLVDSLKFAVLMWVFTYVGALFNGLTLLIXALISLFSIPVIYERHQAQIDHYLGLANKSV 180

Query: 181 KDAMAKIQAKIPGLKRKAD 199
           KDAM KIQAKIPG +R+A+
Sbjct: 181 KDAMGKIQAKIPGFERRAE 199

CPU time:     0.01 user secs.        0.00 sys. secs      0.01 total secs.

Lambda      K       H
   0.325    0.139    0.395
```

Gapped
Lambda K H
0.267 0.0410 0.140

Matrix: BLOSUM62
Gap Penalties: Existence: 11, Extension: 1
Number of Sequences: 1
Number of Hits to DB: 425
Number of extensions: 171
Number of successful extensions: 1
Number of sequences better than 10.0: 1
Number of HSP's better than 10.0 without gapping: 1
Number of HSP's gapped: 1
Number of HSP's successfully gapped: 1
Number of extra gapped extensions for HSPs above 10.0: 0
Length of query: 199
Length of database: 957,198,397
Length adjustment: 125
Effective length of query: 74
Effective length of database: 957,198,272
Effective search space: 70832672128
Effective search space used: 70832672128
Neighboring words threshold: 9
Window for multiple hits: 0
X1: 15 (7.0 bits)
X2: 129 (49.7 bits)
X3: 129 (49.7 bits)
S1: 40 (21.6 bits)
S2: 73 (32.7 bits)

EXHIBIT C

Summary Of Nogo Hydrophilicity Analysis

Analysis No.	Amino Acid Sequence of Interest ("I")	Analyzed Amino Acid Sequence ("A")	Amino Acid positions of I in A	Point Of Greatest Local Hydrophilicity
1	SEQ ID NO:2	entire sequence of interest	aa 1-1163	Peaks throughout the protein
2	amino acids 1-171 fused to amino acids 975-1163 of SEQ ID NO:2	entire sequence of interest	aa 1-172 in the blot corresponding to 1-172 of SEQ ID NO:2 and aa 173-361 in the blot corresponding to aa 976-1163 of SEQ ID NO:2	ca. aa 45
3	SEQ ID NO:29	entire sequence of interest	1-1178	Peaks throughout the protein
4	amino acids 1-172 fused to amino acids 990-1178 of SEQ ID NO:29	entire sequence of interest	aa 1-172 in the blot corresponding to 1-172 of SEQ ID NO:29 and aa 173-361 in the blot corresponding to aa 990-1178 of SEQ ID NO:29	ca. aa 45
5	amino acids 990-1178 of SEQ ID NO:29	entire sequence of interest	aa 1-189 in the blot corresponding to aa 990-1178 of SEQ ID NO:29	ca. aa 13; ca. 65; and others
6	amino acids 975-1163 of SEQ ID NO:2	entire sequence of interest	aa 1-188 in the blot corresponding to aa 976-1163 of SEQ ID NO:2	ca. aa 13; ca. 65; and others
7	SEQ ID NO:32	entire sequence of interest	aa 1-199	Peaks throughout the protein

ProtScale

User-provided sequence:

```
      1          11         21         31         41         51
      |          |          |          |          |          |
    1 MEDIDQSSLV SSSTDSPPRP PPAFKYQFVT EPEDEEDEEE EEDEEEDDED LEELEVLERK    60
   61 PAAGLSAAAV PPAAAAPLLD FSSDSVPPAP RGPLPAAPPA APERQPSWER SPAAPAPSLP   120
  121 PAAAVLPSKL PEDDEPPARP PPPPPAGASP LAEPAAPPST PAAPKRRGSG SVDETLFALP   180
  181 AASEPVIPSS AEKIMDLMEQ PGNTVSSGQE DFPSVLLETA ASLPSLSPLS TVSFKEHGYL   240
  241 GNLSAVSSSE GTIEETLNEA SKELPERATN PFVNRDLAEF SELEYSEMGS SFKGSPKGES   300
  301 AILVENTKEE VIVRSKDKED LVCSAALHSP QESPVGKEDR VVSPEKTMDI FNEMQMSVVA   360
  361 PVREEYADFK PFEQAWEVKD TYEGSRDVLA ARANVESKVD RKCLEDSLEQ KSLGKDSEGR   420
  421 NEDASFPSTP EPVKDSSRAY ITCASFTSAT ESTTANTFPL LEDHTSENKT DEKKIEERKA   480
  481 QIITEKTSPK TSNPFLVAVQ DSEADYVTTD TLSKVTEAAV SNMPEGLTPD LVQEACESEL   540
  541 NEATGTKIAY ETKVDLVQTS EAIQESLYPT AQLCPSFEEA EATPSPVLPD IVMEAPLNSL   600
  601 LPSAGASVVQ PSVSPLEAPP PVSYDSIKLE PENPPPYEEA MNVALKALGT KEGIKEPESF   660
  661 NAAVQETEAP YISIACDLIK ETKLSTEPSP DFSNYSEIAK FEKSVPEHAE LVEDSSPESE   720
  721 PVDLFSDDSI PEVPQTQEEA VMLMKESLTE VSETVAQHKE ERLSASPQEL GKPYLESFQP   780
  781 NLHSTKDAAS NDIPTLTKKE KISLQMEEFN TAIYSNDDLL SSKEDKIKES ETFSDSSPIE   840
  841 IIDEFPTFVS AKDDSPKLAK EYTDLEVSDK SEIANIQSGA DSLPCLELPC DLSFKNIYPK   900
  901 DEVHVSDEFS ENRSSVSKAS ISPSNVSALE PQTEMGSIVK SKSLTKEAEK KLPSDTEKED   960
  961 RSLSAVLSAE LSKTSVVDLL YWRDIKKTGV VFGASLFLLL SLTVFSIVSV TAYIALALLS  1020
 1021 VTISFRIYKG VIQAIQKSDE GHPFRAYLES EVAISEELVQ KYSNSALGHV NSTIKELRRL  1080
 1081 FLVDDLVDSL KFAVLMWVFT YVGALFNGLT LLILALISLF SIPVIYERHQ VQIDHYLGLA  1140
 1141 NKSVKDAMAK IQAKIPGLKR KAD
```

SEQUENCE LENGTH: 1163

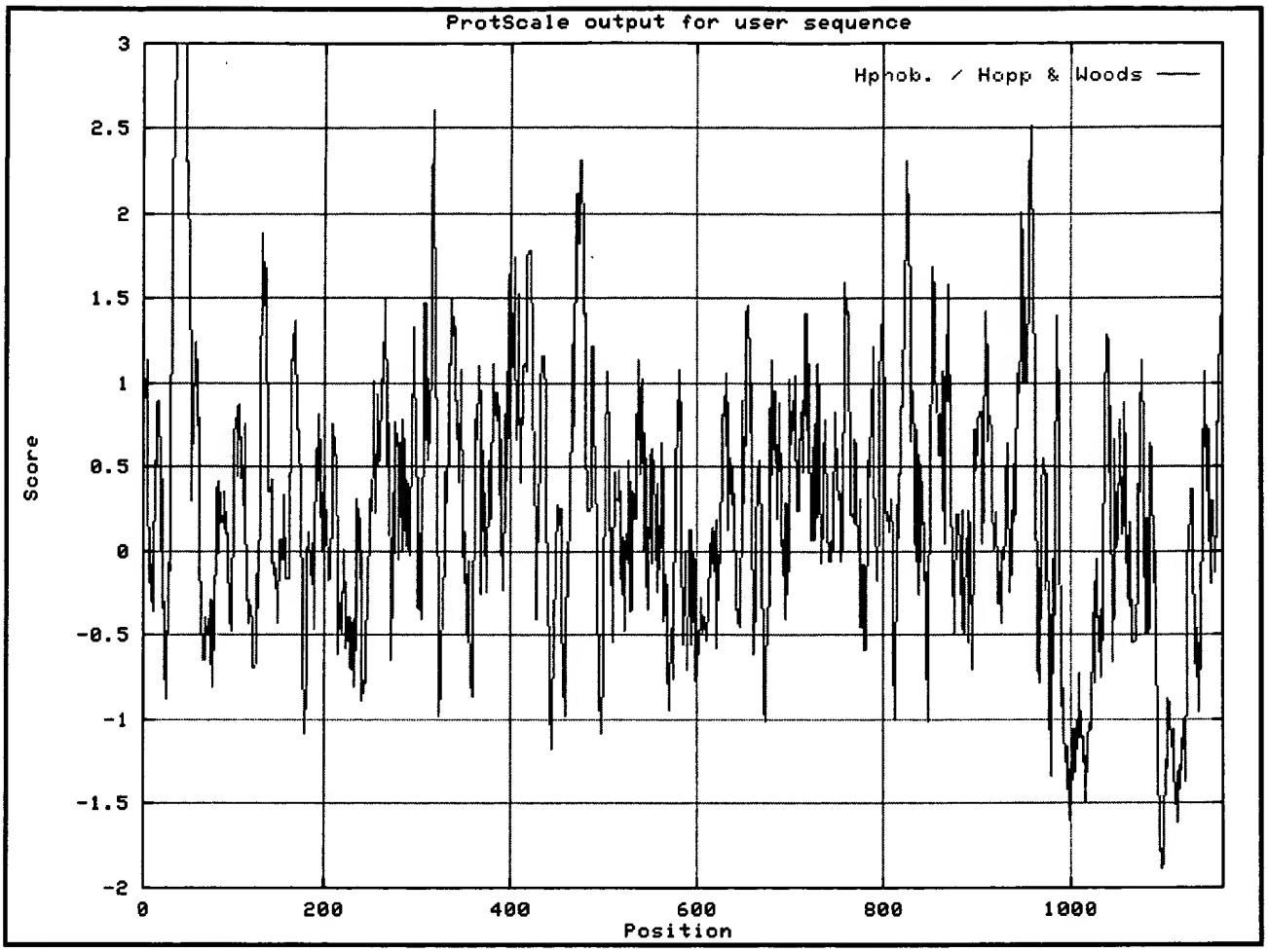
Using the scale **Hphob. / Hopp & Woods**, the individual values for the 20 amino acids are:

```
Ala: -0.500  Arg:  3.000  Asn:  0.200  Asp:  3.000  Cys: -1.000  Gln:  0.200
Glu:  3.000  Gly:  0.000  His: -0.500  Ile: -1.800  Leu: -1.800  Lys:  3.000
Met: -1.300  Phe: -2.500  Pro:  0.000  Ser:  0.300  Thr: -0.400  Trp: -3.400
Tyr: -2.300  Val: -1.500  Asx:  1.600  Glx:  1.600  Xaa: -0.215
```

Weights for window positions 1,..,7, using **linear weight variation model**:

```
   1     2     3     4     5     6     7
1.00  1.00  1.00  1.00  1.00  1.00  1.00
edge              center              edge
```

MIN: -1.886
MAX: 3.000



The results of your ProtScale query are available in the following formats:

- Image in GIF-format
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ProtScale

User-provided sequence:

```
      1          11         21         31         41         51
      |          |          |          |          |          |
    1 MEDIDQSSLV SSSTDSPPRP PPAFKYQFVT EPEDEEDEEE EEDEEEDDED LEELEVLERK    60
   61 PAAGLSAAAV PPAAAAPLLD FSSDSVPPAP RGPLPAAPPA APERQPSWER SPAAPAPSLP   120
  121 PAAAVLPSKL PEDDEPPARP PPPPPAGASP LAEPAAPPST PAAPKRRGSG SVVVDLLYWR   180
  181 DIKKTGVVFG ASLFLLLSLT VFSIVSVTAY IALALLSVTI SFRIYKGVIQ AIQKSDEGHP   240
  241 FRAYLESEVA ISEELVQKYS NSALGHVNST IKELRRLFLV DDLVDSLKFA VLMWVFTYVG   300
  301 ALFNGLTLLI LALISLFSIP VIYERHQVQI DHYLGLANKS VKDAMAKIQA KIPGLKRKAD
```

SEQUENCE LENGTH: 360

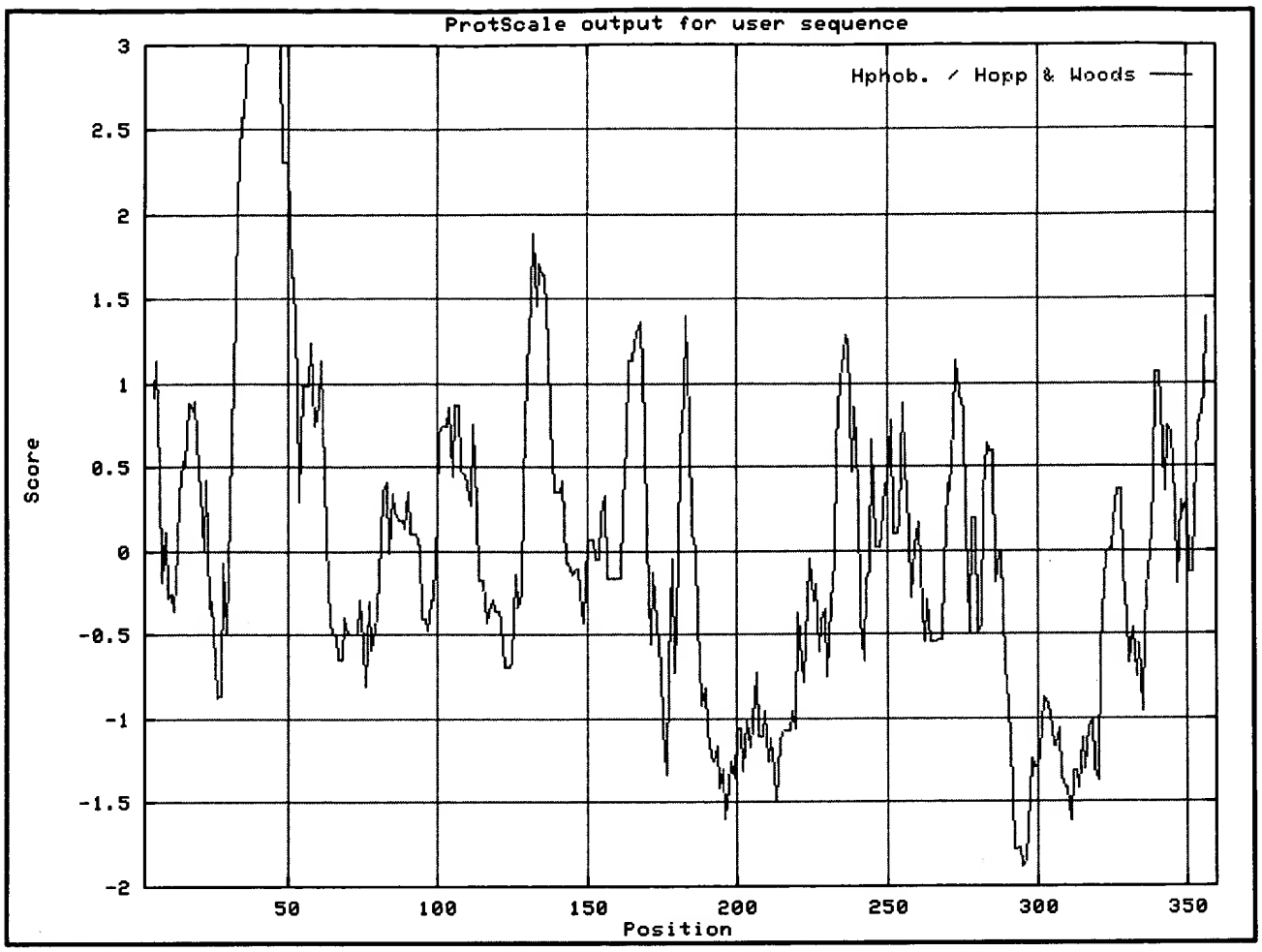
Using the scale **Hphob. / Hopp & Woods**, the individual values for the 20 amino acids are:

```
Ala: -0.500  Arg:  3.000  Asn:  0.200  Asp:  3.000  Cys: -1.000  Gln:  0.200
Glu:  3.000  Gly:  0.000  His: -0.500  Ile: -1.800  Leu: -1.800  Lys:  3.000
Met: -1.300  Phe: -2.500  Pro:  0.000  Ser:  0.300  Thr: -0.400  Trp: -3.400
Tyr: -2.300  Val: -1.500  Asx:  1.600  Glx:  1.600  Xaa: -0.215
```

Weights for window positions 1,..,7, using **linear weight variation model**:

```
   1     2     3     4     5     6     7
1.00  1.00  1.00  1.00  1.00  1.00  1.00
edge              center              edge
```

```
MIN: -1.886
MAX: 3.000
```



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ProtScale

User-provided sequence:

```
      1          11         21         31         41         51
      |          |          |          |          |          |
    1 MEDLDQSPLV SSSDSPPRPQ PAFKYQFVRE PEDEEEEEEE EEEDEDEDLE ELEVLERKPA    60
   61 AGLSAAPVPT APAAGAPLMD FGNDFVPPAP RGPLPAAPPV APERQPSWDP SPVSSTVPAP   120
  121 SPLSAAAVSP SKLPEDDEPP ARPPPPPPAS VSPQAEPVWT PPAPAPAAPP STPAAPKRRG   180
  181 SSGAVVXXXX KIMDLKEQPG NTISAGQEDF PSVLLETAAS XPSLSPLSAA SFKEHEYLGN   240
  241 LSTVLPTEGT LQENVSEASK EVSEKAKTLL IDRDLTEFSE LEYSEMGSSF SVSPKAESAV   300
  301 IVANPREEII VKNKDEEEKL VSNNILHXQQ ELPTALTKLV KEDEVVSSEK AKDSFNEKRV   360
  361 AVEAPMREEY ADFKPFERVW EVKDSKEDSD MLAAGGKIES NLESKVDKKC FADSLEQTNH   420
  421 EKDSESSNDD TSFPSTPEGI KDRSGAYITC APFNPAATES IATNIFPLLE DPTSENXTDE   480
  481 KKIEEKKAQI VTEKNTSTKT SNPFFVAAQD SETDYVTTDN LTKVTEEVVA NMPEGLTPDL   540
  541 VQEACESELN EVTGTKIAYE TKMDLVQTSE VMQESLYPAA QLCPSFEESE ATPSPVLPDI   600
  601 VMEAPLNSAV PSAGASVIQP SSSPLEASSV NYESIKHEPE NPPPYEEAMS VSLKVSGIKE   660
  661 EIKEPENINA ALQETEAPYI SIACDLIKET KLSAEPAPDF SDYSEMAKVE QPVPDHSELV   720
  721 EDSSPDSEPV DLFSDDSIPD VPQKQDETVM LVKESLTETS FESMIEYENK EKLSALPPEG   780
  781 GKPYLESFKL SLDNTKDTLL PDEVSTLSKK EKIPLQMEEL STAVYSNDDL FISKEAQIRE   840
  841 TETFSDSSPI EIIDEFPTLI SSKTDSFSKL AREYTDLEVS HKSEIANAPD GAGSLPCTEL   900
  901 PHDLSLKNIQ PKVEEKISFS DDFSKNGSAT SKVLLLPPDV SALGHTQAEI ESIVKPKVLE   960
  961 KEAEKKLPSD TEKEDRSPSA IFSADLGKTS VVDLLYWRDI KKTGVVFGAS LFLLLSLTVF  1020
 1021 SIVSVTAYIA LALLSVTISF RIYKGVIQAI QKSDEGHPFR AYLESEVAIS EELVQKYSNS  1080
 1081 ALGHVNCTIK ELRRLFLVDD LVDSLKFAVL MWVFTYVGAL FNGLTLLILA LISLFSVPVI  1140
 1141 YERHQAQIDH YLGLANKNVK DAMAKIQAKI PGLKRKAE
```

SEQUENCE LENGTH: 1178

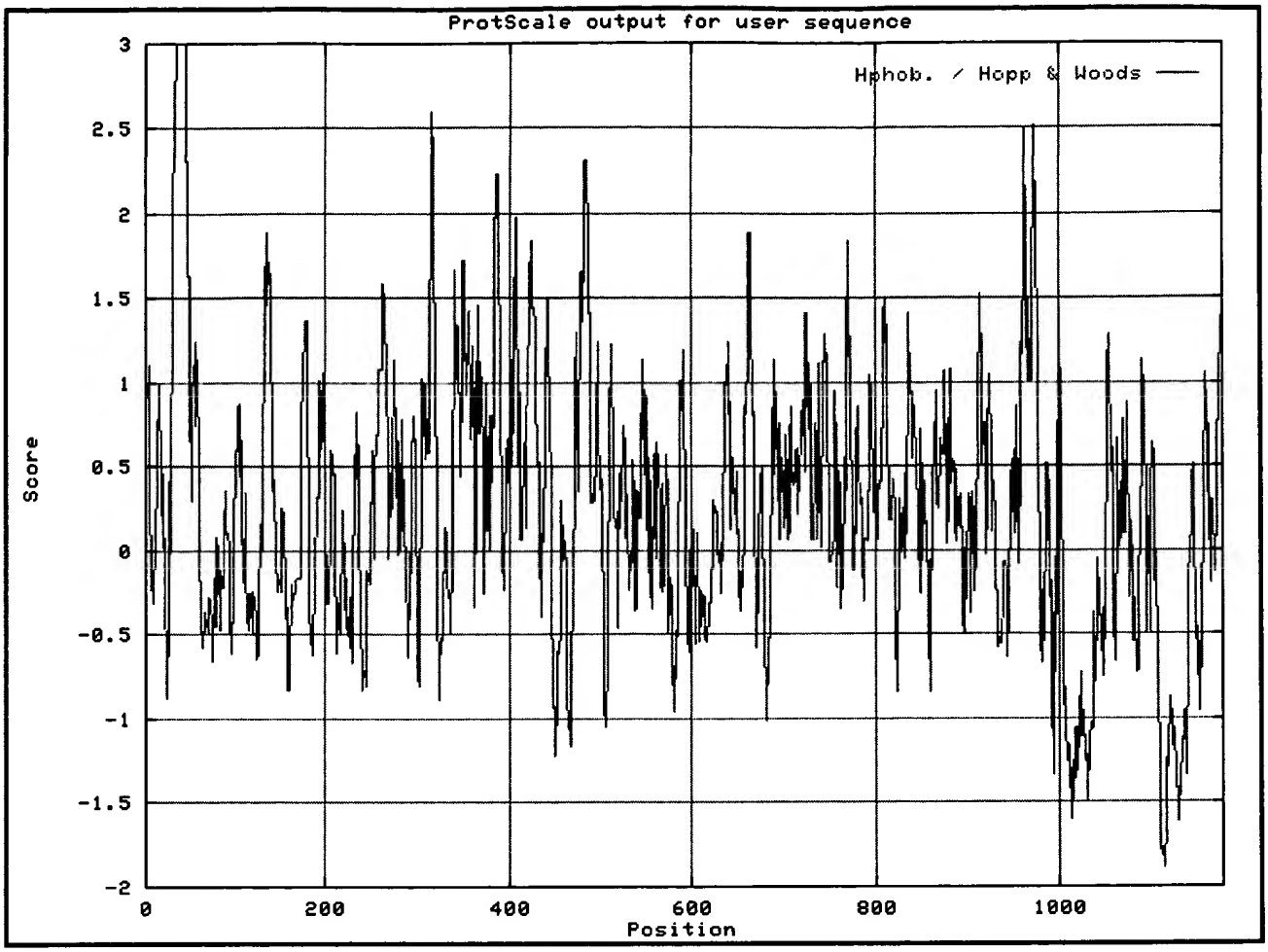
Using the scale **Hphob. / Hopp & Woods**, the individual values for the 20 amino acids are:

```
Ala: -0.500  Arg:  3.000  Asn:  0.200  Asp:  3.000  Cys: -1.000  Gln:  0.200
Glu:  3.000  Gly:  0.000  His: -0.500  Ile: -1.800  Leu: -1.800  Lys:  3.000
Met: -1.300  Phe: -2.500  Pro:  0.000  Ser:  0.300  Thr: -0.400  Trp: -3.400
Tyr: -2.300  Val: -1.500  Asx:  1.600  Glx:  1.600  Xaa: -0.215
```

Weights for window positions 1,..,7, using **linear weight variation model**:

```
   1     2     3     4     5     6     7
1.00  1.00  1.00  1.00  1.00  1.00  1.00
edge              center              edge
```

MIN: -1.886
MAX: 3.000



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ProtScale

User-provided sequence:

```
      1          11         21         31         41         51
      |          |          |          |          |          |
    1 MEDLDQSPLV SSSDSPPRPQ PAFKYQFVRE PEDEEEEEEE EEEDEDEDLE ELEVLERKPA    60
   61 AGLSAAPVPT APAAGAPLMD FGNDFVPPAP RGPLPAAPPV APERQPSWDP SPVSSTVPAP   120
  121 SPLSAAAVSP SKLPEDDEPP ARPPPPPPAS VSPQAEPVWT PPAPAPAAPP STSVVDLLYW   180
  181 RDIKKTGVVF GASLFLLLSL TVFSIVSVTA YIALALLSVT ISFRIYKGVI QAIQKSDEGH   240
  241 PFRAYLESEV AISEELVQKY SNSALGHVNC TIKELRRLFL VDDLVDSLKF AVLMWVFTYV   300
  301 GALFNGLTLL ILALISLFSV PVIYERHQAQ IDHYLGLANK NVKDAMAKIQ AKIPGLKRKA   360
  361 E
```

SEQUENCE LENGTH: 361

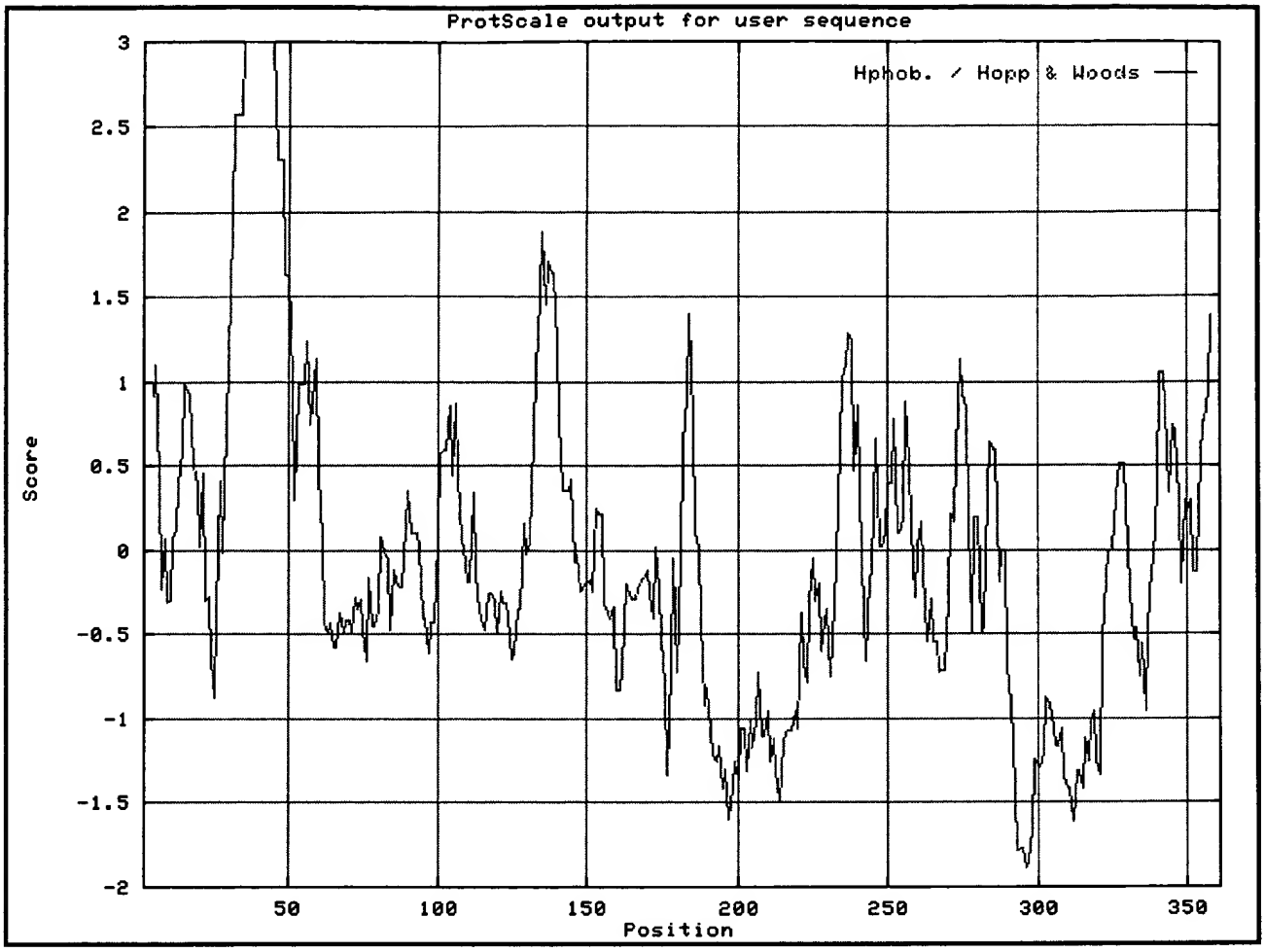
Using the scale **Hphob. / Hopp & Woods**, the individual values for the 20 amino acids are:

```
Ala: -0.500  Arg:  3.000  Asn:  0.200  Asp:  3.000  Cys: -1.000  Gln:  0.200
Glu:  3.000  Gly:  0.000  His: -0.500  Ile: -1.800  Leu: -1.800  Lys:  3.000
Met: -1.300  Phe: -2.500  Pro:  0.000  Ser:  0.300  Thr: -0.400  Trp: -3.400
Tyr: -2.300  Val: -1.500  Asx:  1.600  Glx:  1.600  Xaa: -0.215
```

Weights for window positions 1,..,7, using **linear weight variation model**:

```
   1     2     3     4     5     6     7
1.00  1.00  1.00  1.00  1.00  1.00  1.00
edge              center              edge
```

```
MIN: -1.886
MAX: 3.000
```



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ProtScale

User-provided sequence:

```
      1          11         21         31         41         51
      |          |          |          |          |          |
    1 SVVDLLYWRD IKKTGVVFGA SLFLLLSLTV FSIVSVTAYI ALALLSVTIS FRIYKGVIQA    60
   61 IQKSDEGHPF RAYLESEVAI SEELVQKYSN SALGHVNCTI KELRRLFLVD DLVDSLKFAV   120
  121 LMWVFTYVGA LFNGLTLLIL ALISLFSVPV IYERHQAQID HYLGLANKNV KDAMAKIQAK   180
  181 IPGLKRKAE
```

SEQUENCE LENGTH: 189

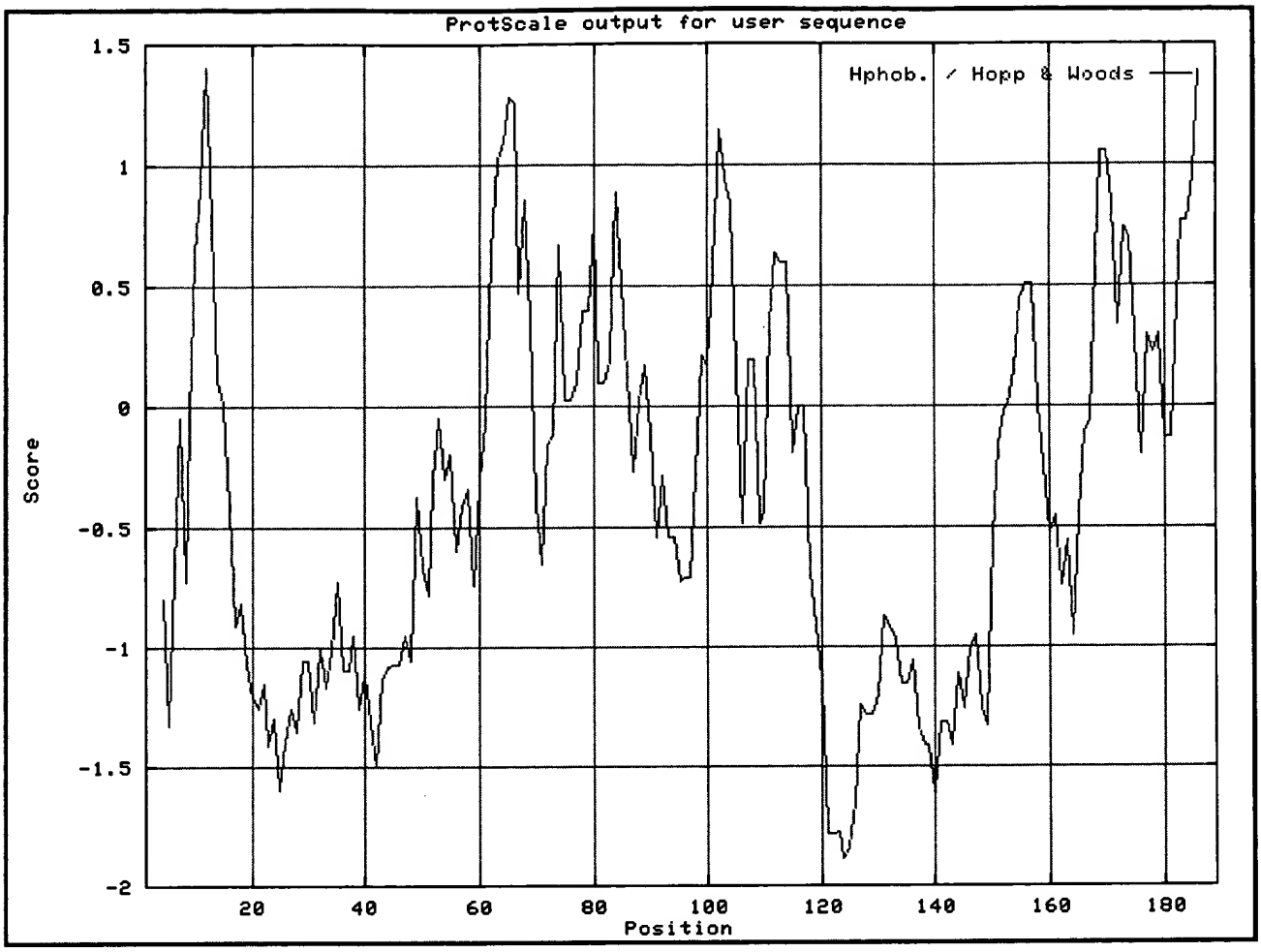
Using the scale **Hphob. / Hopp & Woods**, the individual values for the 20 amino acids are:

```
Ala: -0.500  Arg:  3.000  Asn:  0.200  Asp:  3.000  Cys: -1.000  Gln:  0.200
Glu:  3.000  Gly:  0.000  His: -0.500  Ile: -1.800  Leu: -1.800  Lys:  3.000
Met: -1.300  Phe: -2.500  Pro:  0.000  Ser:  0.300  Thr: -0.400  Trp: -3.400
Tyr: -2.300  Val: -1.500  Asx:  1.600  Glx:  1.600  Xaa: -0.215
```

Weights for window positions 1,..,7, using **linear weight variation model**:

```
   1     2     3     4     5     6     7
1.00  1.00  1.00  1.00  1.00  1.00  1.00
edge              center              edge
```

```
MIN: -1.886
MAX: 1.400
```



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ProtScale

User-provided sequence:

```
      1          11         21         31         41         51
      |          |          |          |          |          |
    1 VVDLLYWRDI KKTGVVFGAS LFLLLSLTVF SIVSVTAYIA LALLSVTISF RIYKGVIQAI    60
   61 QKSDEGHPFR AYLESEVAIS EELVQKYSNS ALGHVNSTIK ELRRLFLVDD LVDSLKFAVL   120
  121 MWVFTYVGAL FNGLTLLILA LISLFSIPVI YERHQVQIDH YLGLANKSVK DAMAKIQAKI   180
  181 PGLKRKAD

SEQUENCE LENGTH: 188
```

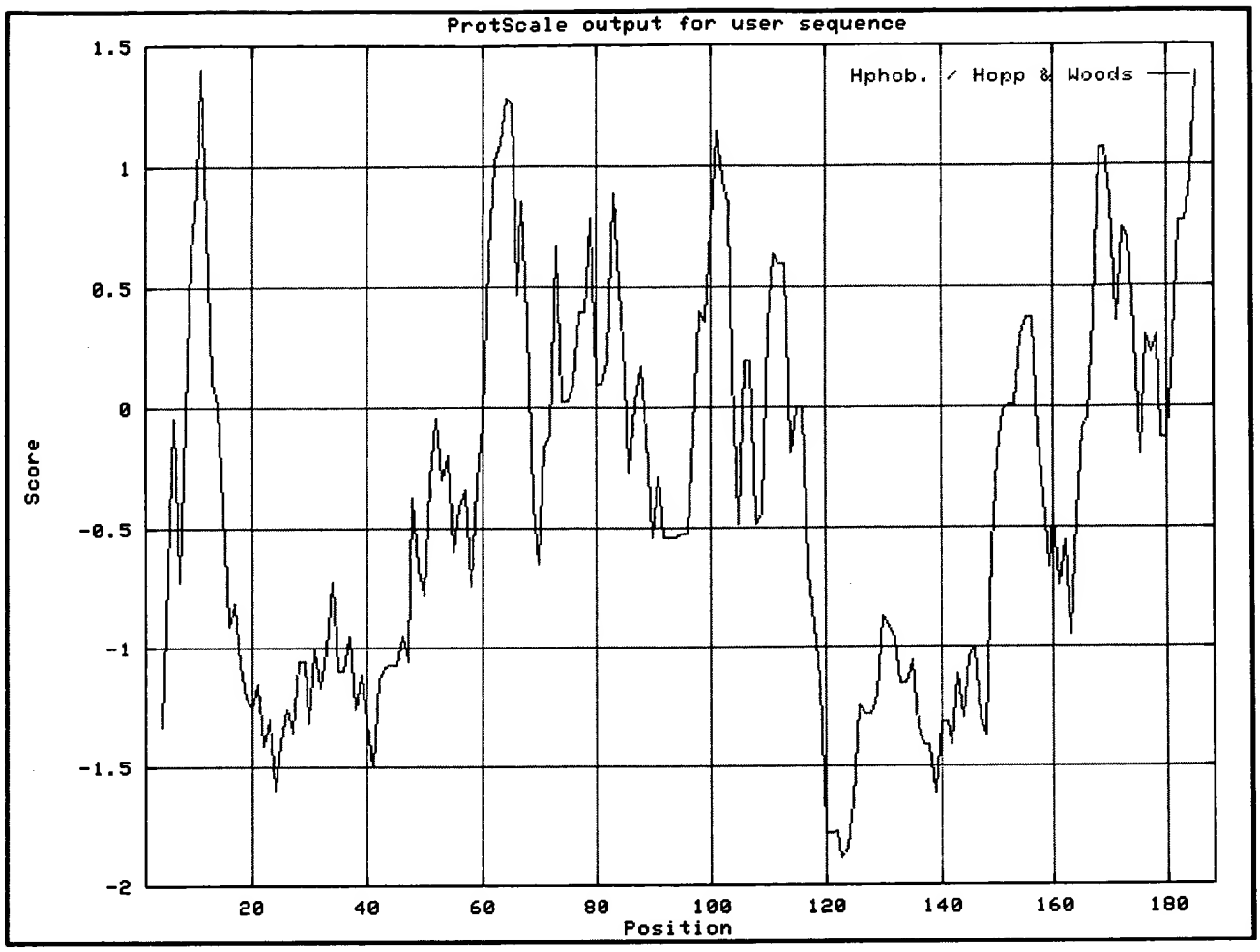
Using the scale **Hphob. / Hopp & Woods**, the individual values for the 20 amino acids are:

```
Ala: -0.500  Arg:  3.000  Asn:  0.200  Asp:  3.000  Cys: -1.000  Gln:  0.200
Glu:  3.000  Gly:  0.000  His: -0.500  Ile: -1.800  Leu: -1.800  Lys:  3.000
Met: -1.300  Phe: -2.500  Pro:  0.000  Ser:  0.300  Thr: -0.400  Trp: -3.400
Tyr: -2.300  Val: -1.500  Asx:  1.600  Glx:  1.600  Xaa: -0.215
```

Weights for window positions 1,..,7, using **linear weight variation model**:

```
   1     2     3     4     5     6     7
1.00  1.00  1.00  1.00  1.00  1.00  1.00
edge              center              edge
```

```
MIN: -1.886
MAX: 1.400
```



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ProtScale

User-provided sequence:

```
      1          11         21         31         41         51
      |          |          |          |          |          |
    1 MDGQKKHWKD KVVDLLYWRD IKKTGVVFGA SLFLLLSLTV FSIVSVTAYI ALALLSVTIS    60
   61 FRIYKGVIQA IQKSDEGHPF RAYLESEVAI SEELVQKYSN SALGHVNSTI KELRRLFLVD   120
  121 DLVDSLKFAV LMWVFTYVGA LFNGLTLLIL ALISLFSIPV IYERHQVQID HYLGLANKSV   180
  181 KDAMAKIQAK IPGLKRKAD

SEQUENCE LENGTH: 199
```

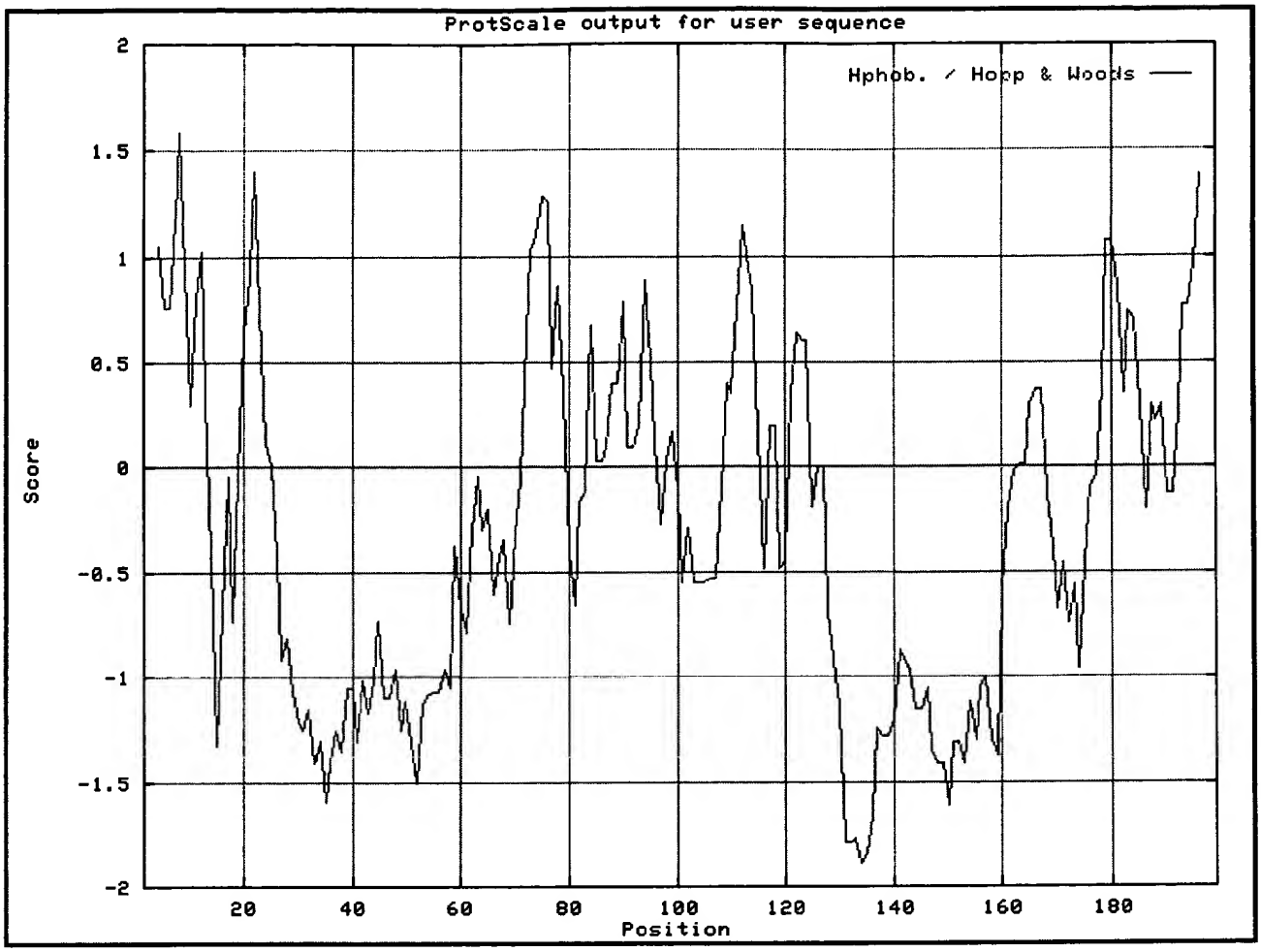
Using the scale **Hphob. / Hopp & Woods**, the individual values for the 20 amino acids are:

```
Ala: -0.500  Arg:  3.000  Asn:  0.200  Asp:  3.000  Cys: -1.000  Gln:  0.200
Glu:  3.000  Gly:  0.000  His: -0.500  Ile: -1.800  Leu: -1.800  Lys:  3.000
Met: -1.300  Phe: -2.500  Pro:  0.000  Ser:  0.300  Thr: -0.400  Trp: -3.400
Tyr: -2.300  Val: -1.500  Asx:  1.600  Glx:  1.600  Xaa: -0.215
```

Weights for window positions 1,..,7, using **linear weight variation model**:

```
   1     2     3     4     5     6     7
1.00  1.00  1.00  1.00  1.00  1.00  1.00
edge              center              edge
```

```
MIN: -1.886
MAX: 1.586
```



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